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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,743	05/26/2005	Hiroyuki Osada	1261-1056PUS1	6909

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
CHENG, KAREN	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 11/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/516,743	OSADA ET AL.	
	Examiner	Art Unit	
	Karen Cheng	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4,8 and 9 is/are rejected.

7)☒ Claim(s) 5 and 9 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 12/6/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 are currently pending in the instant application.

Information Disclosure Statement

Applicant's Information Disclosure Statement filed on Nov. 12, 2003 has been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

Priority

The application is a 371 of International Application No. PCT/JP03/07189, filed on 6/06/2003, which claims the benefit of foreign priority under 35 U.S.C. 119, to Japan Foreign Application No. 2002-166868, filed on 06/07/2002

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

The nature of the invention

The nature of the invention is directed to a pharmaceutical composition containing a compound, which is an antitumor agent.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent diseases such as cancer tumors). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that that contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any preventive regimen on its fact.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The burden of

enabling one skilled in the art to prevent a disease would be much greater than that of enabling the treatment of such a disease. In the instant case, the specification does not provide sufficient guidance as to how one skilled in the art would accomplish the objective of treating or preventing tumors. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for treating or preventing tumors *in vivo*.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified could actually treat or prevent a tumor.

"To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compositions can be administered to order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of subjects who have the potential of becoming afflicted with cancer tumors.

Since applicants "preventive" assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. Applicants have not provided any competent evidence or disclosed test results that are highly predictive for the pharmaceutical use of preventing any disease. Hence, one of skill in the art is unable to fully predict possible preventive results from the administration of the claimed

compound due to the absence of convincing evidence that said composition has an effect on any.

The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types and that cancer classification has been based primarily on morphological appearance of the tumor. Tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531). Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Hortobagyi, p. 974) that the several genes, including p53, bcl-2, c-myc, and c-myb, HER-2/neu, and cyclin D, have all been found in abnormal levels in patients with breast cancer. However, the number and types of mutations necessary for development of breast cancer are not known. These examples illustrate the different cellular mechanisms believed to be involved in the progression of cancer, and thus showcase the unpredictability in the art, especially in regards to treatment protocols. While epolactaene has been shown to have potent neurite outgrowth activity in human neuroblastoma cell lines, there are no results to show its activity as antitumor agent in any other types of cells.

The amount of direction or guidance present and the presence or absence of working examples

The specification describes the use of the claimed compound in measuring the cell count of human neuroblastoma cells *in vitro* on p. 39.

The breadth of the claims

The instant breadth of the rejected claim is broader than the disclosure, specifically, the instant claim include prevention or treatment of cancers or tumors. However the specification only provides evidence for the inhibitory effect of the compound on cells of human neuroblastoma.

The quantity or experimentation needed and the level of skill in the art

It would require undue experimentation of one of ordinary skill in the art to ascertain the effectiveness of the compound in the treatment or prevention of tumors. Factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of treating or preventing cancer tumors, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in cope with the claims.

In consideration of each of the 8 factors, it is apparent that undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent

factual data to the contrary, the amount and level of experimentation needed is undue. Therefore, claim 9 is rejected under 35 U.S.C. § 112, 1st paragraph.

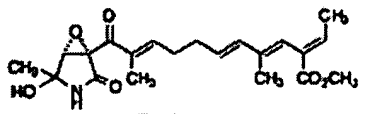
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hayashi and Narasaka (Chemistry Letters, 1998, p. 313-314) and Kuramochi *et al* (Tetrahedron Letters, *40*, 1999, p.7371-7374).

Hayashi and Narasaka disclose the compound epolactaene on p.313. Kuramochi *et al* disclose the same compound on p. 7373.



Epolactaene

The prior art corresponds to applicants' claimed compound of formula I where R = methyl.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

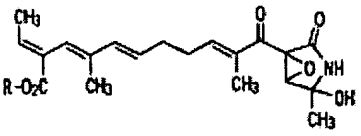
invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashi and Narasaka (Chemistry Letters, 1998, p. 313-314).

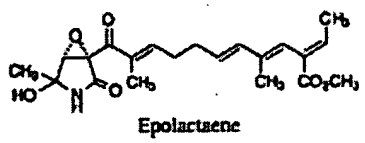
Applicants' instant elected invention in claims 1-4, 8 and 9 teach preparation of



wherein R represents a linear, branched, or cyclic alkyl group having 1 to 6 carbon atoms.

Determination of the scope and content of the prior art (MPEP §2141.01)

Hayashi *et al* teach the preparation of

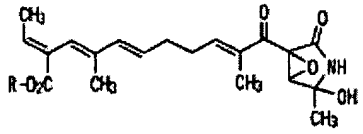


Epolactaene

wherein R is Me.

Ascertainment of the different between the prior art and the claims (MPEP §2141.02)

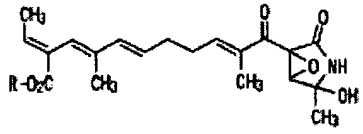
The difference between the prior art of Hayashi *et al* and the instantly claimed compounds of applicant is that the invention of Hayashi *et al* is directed to preparation of a compound of formula



where R represents methyl rather than R = linear, branched, or cyclic alkyl group having 1 to 6 carbon atoms claimed in the instant invention.

Finding of prima facie obviousness- rational and motivation (MPEP §2142-2143)

Hayashi *et al* is analogous art because the compounds of the structural formula



where R is an ethyl, propyl, etc would be considered analogous art. Adjacent homologues and structural isomers are generally so structurally similar that "without more" such structural similarity could give rise to prima facie obviousness. In re Wilder, 563 F.2d 457, 195 USPQ 426. For example, the substitution of a CH_3 for a H group on the $-CO_2Me$ would lead to a CO_2Et, and in re Wood, 199 USPQ 137, hydrogen and methyl are deemed obvious variants. In the absence of unexpected results, one skilled in the art would expect that the instant claims which contain compounds that are analogous to the compounds of Hayashi *et al*, i.e. adjacent homologues of the CO_2R where R = Me, is prima facie. The motivation to make the claimed compounds derives from the expectation that structurally similar

compounds are generally expected to have similar properties and have similar utilities. The explicit teaching of Hayashi *et al* together with the enabled examples would have motivated one skilled in the art to modify the known compounds with such generic teaching with the expectation that they would all have similar activity as taught by Hayashi *et al*.

Claim Objections

Claim 5 is objected to as being dependent upon a rejected base claim, but would appear allowable over the prior art of record if rewritten in independent form to include all of the limitations of the base claim and any intervening claims.

Claim 9 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 8. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). A pharmaceutical composition's intended use does not further limit the claim.

Objections: Content of Specification

The specification does not incorporate cross reference to related applications. The specification should contain the following sections below, as applicable:

b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cheng whose telephone number is 571-272-6233. The examiner can normally be reached on M-F, 9AM to 5:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen Cheng
Patent Examiner, AU 1626

REBECCA ANDERSON
PATENT EXAMINER

Joseph McKane
Supervisory Patent Examiner, AU 1626